Original Article

Laboratory Survey of Antibiotic Nonsusceptibility among *Streptococcus pneumoniae* Isolates in South Carolina, 1998 versus 2000

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Background: In 1998, the South Carolina Department of Health and Environmental Control surveyed clinical microbiology laboratories statewide to determine the prevalence of antibiotic nonsusceptibility among isolates of *Streptococcus pneumoniae*. A follow-up study was conducted in 2001.

Methods: A cross-sectional study was conducted to estimate the prevalence of penicillin nonsusceptibility (PCN-N), extended-spectrum cephalosporin nonsusceptibility (ESC-N), and levofloxacin nonsusceptibility (LEV-N) in South Carolina. A standardized questionnaire was mailed to 89 laboratories.

Results: The prevalence of penicillin intermediate resistance increased from 1998 (17.6%) to 2000 (20.9%, χ^2 $P = 0.008$). Furthermore, the prevalence of PCN-N increased from 1998 (34.5%) to 2000 (38.4%, χ^2 $P = 0.01$). The prevalence of ECN-N decreased from 1998 (19.1%) to 2000 (17.7%), but the difference was not significant (χ^2 $P = 0.25$).

Conclusion: The laboratory survey was a low-cost method of estimating the change in prevalence of antibiotic nonsusceptibility, and it emphasizes regional surveillance because the prevalence of antibiotic nonsusceptibility varied geographically.

Key Words: antibiotic resistance, laboratory testing, *Streptococcus pneumoniae*, surveillance

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Streptococcus pneumoniae is a leading cause of potentially life-threatening community-acquired diseases in the United States[1–4] and accounts for more deaths than any other vaccine-preventable bacterial disease.[5] *S. pneumoniae* is the most common cause of community-acquired pneumonia, meningitis, acute otitis media, and sinusitis.[6–9] Community-acquired infections with drug-resistant *S. pneumoniae* (DRSP) have emerged as a major public health concern in the United States,[10–12] with a major contribution being increased use of antibiotics, both appropriate and inappropriate.

The emergence of DRSP underscores the need for timely, local, population-based surveillance of antibiotic resistance. In 1998, the South Carolina Department of Health and Environmental Control (DHEC) surveyed clinical microbiology laboratories statewide to determine the extent of screening and antimicrobial susceptibility testing of *S. pneumoniae* and the prevalence of penicillin nonsusceptibility (PCN-N) and extended-spectrum cephalosporin nonsusceptibility (ESC-N).

Key Points

- The prevalence of penicillin nonsusceptibility (PCN-N) was 38.4%, with 20.9% of isolates intermediately resistant and 17.5% high-level resistant. This is a significant increase in PCN-N compared with 1998.
- The prevalence of extended-spectrum cephalosporin nonsusceptibility (ECN-N) was 17.7%, with 11.7% of isolates intermediately resistant and 6.0% high-level resistant. This is a decrease in ECN-N compared with 1998, but it is not significant.
- The prevalence of levofloxacin nonsusceptibility (LEV-N) was 0.8%, with 0.5% of isolates intermediately resistant and 0.3% high-level resistant.
- These results are similar to or higher than recent Centers for Disease Control and Prevention pneumococcal surveillance system data.

The 1998 study reviewed data from January 1, 1998, through September 30, 1998. This article summarizes the results of the follow-up study conducted in 2001 and compares the results with data from the 1998 study. The 2001 survey results will aid in identifying time and geographic trends in resistance rates, as well as in creating guidelines for empiric therapy for practitioners in South Carolina.

Materials and Methods

Study Design

A cross-sectional study of all clinical microbiology laboratories was conducted to estimate the prevalence of PCN-N, ESC-N, and levofloxacin nonsusceptibility (LEV-N) in South Carolina. Data were reported for the period of January 1, 2000, to December 31, 2000.

Survey Instrument

In 2001, the DHEC used an updated version of the 1998 standardized questionnaire that was expanded to include questions pertaining to levofloxacin. A survey was mailed to 89 clinical microbiology laboratories. A postcard reminder was sent as follow-up, and those not responding after the postcard were contacted by telephone. To evaluate compliance with *S. pneumoniae* penicillin susceptibility testing guidelines established by the National Committee for Clinical Laboratory Standards (NCCLS), data were collected on the criteria a laboratory used for selecting specimens, techniques for oxacillin disk diffusion screening, and methods for the determination of penicillin minimum inhibitory concentrations (MICs). Data were also collected on the number of *S. pneumoniae* isolates that were identified during the designated time frame, tested for susceptibility to penicillin, found to be

Table 1. Antibiotic nonsusceptibility among *Streptococcus pneumoniae* isolates in South Carolina, 2000

Prevalence of penicillin nonsusceptibility[a]			
Category (No. of isolates)	**Total nonsusceptible isolates (%)**	**PCN-I[b] (%)**	**PCN-R[c] (%)**
Sterile site isolates (n = 763)	276 (36.2)	119 (15.6)	157 (20.6)
Nonsterile site isolates (n = 1,121)	425 (37.9)	223 (19.9)	202 (18.0)
All isolates (n = 2,470)	948 (38.4)	517 (20.9)	431 (17.5)
Prevalence of extended-spectrum cephalosporin nonsusceptibility[a]			
Category (No. of isolates)	**Total nonsusceptible isolates (%)**	**ESC-I[d] (%)**	**ESC-R[e] (%)**
Sterile site isolates (n = 745)	135 (18.1)	94 (12.6)	41 (5.5)
Nonsterile site isolates (n = 1,070)	210 (19.6)	126 (11.8)	84 (7.8)
All isolates (n = 2,401)	425 (17.7)	282 (11.7)	143 (6.0)
Prevalence of levofloxacin nonsusceptibility[a]			
Category (No. of isolates)	**Total nonsusceptible isolates (%)**	**LEV-I[f] (%)**	**LEV-R[g] (%)**
Sterile site isolates (n = 397)	0 (0)	0 (0)	0 (0)
Nonsterile site isolates (n = 730)	10 (1.4)[h]	7 (1.0)	3 (0.4)
All isolates (n = 1,369)	11 (0.8)	7 (0.5)	4 (0.3)

[a] *Confirmed by MIC test.*

[b] *PCN-I, penicillin intermediate (0.12 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[c] *PCN-R, penicillin high-level resistant (MIC ≥ 2.00 μg/ml).*

[d] *ESC-I, extended-spectrum cephalosporin intermediate (0.50 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[e] *ESC-R, extended-spectrum cephalosporin high-level resistant (MIC ≥ 2.00 μg/ml).*

[f] *LEV-I, levofloxacin intermediate (MIC = 4.00 μg/ml).*

[g] *LEV-R, levofloxacin high-level resistant (MIC ≥ 8.00 μg/ml).*

[h] *Prevalence was higher in nonsterile sites than in sterile sites (Fisher's exact test P = 0.02).*

Table 2. Antibiotic intermediate resistance, high-level resistance, and nonsusceptibility prevalence rates among *Streptococcus pneumoniae* isolates in South Carolina by year

	PCN-I[a]			PCN-R[b]			PCN-N[c]			ESC-I[d]			ESC-R[e]			ESC-N[f]		
	1998	2000	*P* value	1998	2000	*P* value	1998	2000	*P* value	1998	2000	*P* value	1998	2000	*P* value	1998	2000	*P* value
All isolates	17.6	20.9	0.008[g]	16.9	17.5	0.67	34.5	38.4	0.01[g]	13.5	11.8	0.09	5.6	6.0	0.62	19.1	17.7	0.25
Rural counties	14.9	16.7	0.44	14.9	19.5	0.06	29.9	36.2	0.04[g]	9.5	12.4	0.16	5.2	5.6	0.81	14.7	17.9	0.18
Urban counties	18.4	22.4	0.007[g]	17.6	16.8	0.56	36.0	39.1	0.07	14.8	11.6	0.008[g]	5.7	6.1	0.66	20.5	17.6	0.04[g]

[a]*PCN-I, penicillin intermediate (0.12 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[b]*PCN-R, penicillin high-level resistant (MIC ≥ 2.00 μg/ml).*

[c]*PCN-N, penicillin nonsusceptibility.*

[d]*ESC-I, extended-spectrum cephalosporin intermediate (0.50 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[e]*ESC-R, extended-spectrum cephalosporin high-level resistant (MIC ≥ 2.00 μg/ml).*

[f]*ESC-N, extended-spectrum cephalosporin nonsusceptibility.*

[g]*Significant difference detected using a χ^2 test ($P < 0.05$).*

Table 3. Antibiotic nonsusceptibility among *Streptococcus pneumoniae* isolates in rural and urban counties of South Carolina, 2000

Prevalence of penicillin nonsusceptibility[a]

Category (No. of isolates)	Total nonsusceptible isolates (%)	PCN-I[b] (%)	PCN-R[c] (%)
Rural counties (n = 622)	225 (36.2)	104 (16.7)	121 (19.5)
Urban counties (n = 1,848)	723 (39.1)	413 (22.3)	310 (16.8)

Prevalence of extended-spectrum cephalosporin nonsusceptibility[a]

Category (No. of isolates)	Total nonsusceptible isolates (%)	ESC-I[d] (%)	ESC-R[e] (%)
Rural counties (n = 574)	103 (17.9)	71 (12.3)	32 (5.6)
Urban counties (n = 1,827)	322 (17.6)	211 (11.5)	111 (6.1)

Prevalence of levofloxacin nonsusceptibility[a]

Category (No. of isolates)	Total nonsusceptible isolates (%)	LEV-I[f] (%)	LEV-R[g] (%)
Rural counties (n = 369)	3 (0.8)	0 (0.0)	3 (0.8)
Urban counties (n = 1,000)	8 (0.8)	7 (0.7)	1 (0.1)

[a]*Confirmed by MIC test.*

[b]*PCN-I, penicillin intermediate (0.12 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[c]*PCN-R, penicillin high-level resistant (MIC ≥ 2.00 μg/ml).*

[d]*ESC-I, extended-spectrum cephalosporin intermediate (0.50 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[e]*ESC-R, extended-spectrum cephalosporin high-level resistant (MIC ≥ 2.00 μg/ml).*

[f]*LEV-I, levofloxacin intermediate (MIC = 4.00 μg/ml).*

[g]*LEV-R, levofloxacin high-level resistant (MIC ≥ 8.00 μg/ml).*

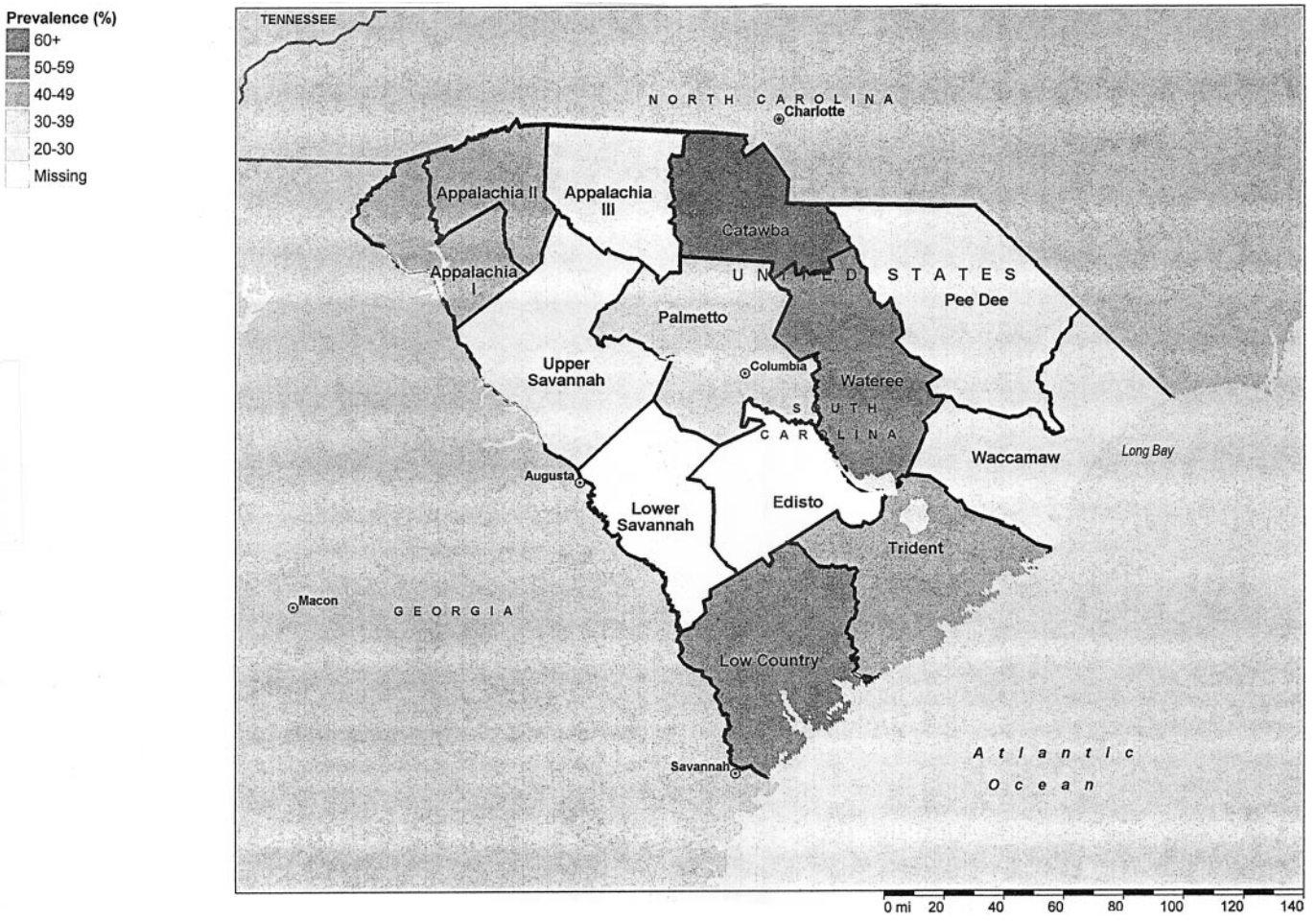

Fig. 1 **Prevalence of penicillin nonsusceptibility by public health district, South Carolina, 2000.**

possibly resistant by the oxacillin disk diffusion test, and resistant by MIC testing distinguishing penicillin intermediate (PCN-I) or penicillin high-level resistant (PCN-R). Questions regarding MIC test results for extended-spectrum cephalosporins and levofloxacin were also included. Information was requested separately for isolates from normally sterile sites (eg, blood, cerebrospinal fluid) and from nonsterile sites (ie, sputum, nasopharyngeal swab).

Data Analysis

Data were entered into EpiInfo Version 6.04b (Centers for Disease Control and Prevention [CDC], Atlanta, GA) and exported to SAS Version 8.2 (SAS Institute, Inc., Cary, NC) for analysis. A χ^2 test was used to detect a significant difference ($P < 0.05$) between prevalence rates. Fisher's exact test was used to detect a significant difference when at least one cell size was less than 5.

Results

Sixty-one (68.5%) of the 89 clinical microbiology laboratories surveyed responded. Thirty-four (73.9%) of the 46 counties in South Carolina were represented in the study. Forty-two (68.9%) of 61 laboratories reported performing some type of antimicrobial susceptibility testing on isolates of *S. pneumoniae*. Seventeen of the 19 (89.5%) laboratories that did not perform some type of antimicrobial susceptibility testing send their *S. pneumoniae* isolates to a reference laboratory for susceptibility testing. Twenty-six (42.6%) laboratories reported using a screening test (ie, disk diffusion with a 1-μg oxacillin disk) to test for penicillin nonsusceptibility in isolates of *S. pneumoniae*. Thirty-three (54.1%) laboratories reported performing MIC tests for PCN-N in *S. pneumoniae*. Eighteen of the 28 (64.3%) laboratories that do not perform MIC testing for PCN-N send their *S. pneumoniae* isolates to a reference laboratory for MIC testing.

Statewide Prevalence

Table 1 summarizes the statewide prevalences of PCN-N, ESC-N, and LEV-N that were calculated using the MIC test result data reported by the laboratories. The prevalence of PCN-N in 2000 was 38.4%. The prevalence of PCN-N was higher in 2000 than in 1998 (34.5%, χ^2 $P = 0.01$). The

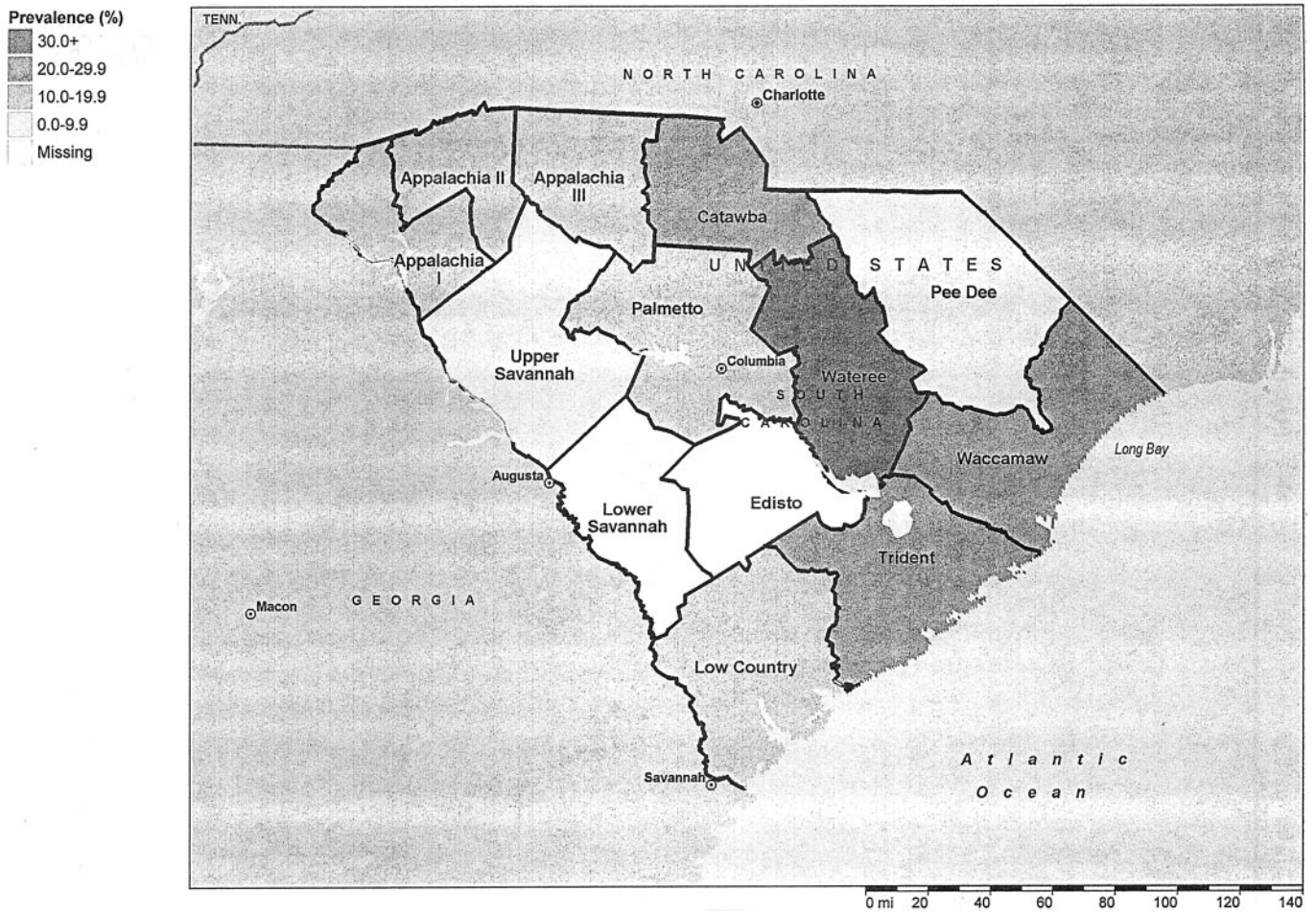

Fig. 2 **Prevalence of cephalosporin nonsusceptibility by public health district, South Carolina, 2000.**

prevalence of ESC-N in 2000 was 17.7%. Although the prevalence of ESC-N decreased from 1998 (19.1%), the difference was not significant (χ^2 $P = 0.25$). The prevalence of LEV-N in 2000 was 0.8%. Data were not collected on levofloxacin MIC test results in 1998. Table 2 summarizes the differences in intermediate resistance, high-level resistance, and nonsusceptibility prevalences among penicillin and extended-spectrum cephalosporins by year.

Site of Infection

The site of infection was given for 1,968 isolates that were tested for PCN-N. One thousand fifty-six (53.7%) isolates were from nonsterile sites (transtracheal, nasopharyngeal, or sputum [1,009 of 1,056]; eye [47 of 1,056]), and 912 (46.3%) were from sterile sites (blood [721 of 912]; middle ear [135 of 912]; pleural, peritoneal, pericardial, or joint fluid [30 of 912]; cerebrospinal fluid [CSF] [26 of 912]). The prevalence of PCN-N did not differ between sterile and nonsterile site isolates (36.2% versus 37.9%, χ^2 $P = 0.44$). The prevalence of ESC-N also did not differ between sterile site isolates and nonsterile site isolates (18.1% versus 19.6%, χ^2 $P = 0.42$). The prevalence of LEV-N was higher in nonsterile site isolates than in sterile site isolates (1.4% versus 0%, Fisher's exact test $P = 0.02$) (Table 1).

Prevalence by Population

In 2000, the prevalences of PCN-N, ESC-N, and LEV-N did not vary significantly by level of urbanization. Counties were classified into two groups, urban and rural, as defined by the Office of Research and Statistics of the South Carolina State Budget and Control Board.[13] Table 3 summarizes the prevalences of PCN-N, ESC-N, and LEV-N by level of urbanization.

Urban Counties. Thirty-five laboratories from 12 urban counties in South Carolina responded to the survey. The prevalence of PCN-N in 2000, based on the MIC test result data, was 39.1%. The prevalence of PCN-N in urban counties increased from 1998 (36.0%) to 2000, but the increase was not significant (χ^2 $P = 0.07$). According to ESC MIC results, the prevalence of ESC-N among pneumococcal isolates in 2000

Table 4. Antibiotic nonsusceptibility among *Streptococcus pneumoniae* isolates from hospitals in Greenville County, South Carolina, 2000

Prevalence of penicillin nonsusceptibility[a]			
Category (No. of isolates)	**Total nonsusceptible isolates (%)**	**PCN-I[b] (%)**	**PCN-R[c] (%)**
Hospital A (n = 247)	133 (53.8)[f]	107 (43.3)	26 (10.5)
Hospital B (n = 29)	10 (34.5)	8 (27.6)	2 (6.9)
Hospital C (n = 100)	30 (30.0)	25 (25.0)	5 (5.0)
Hospital D (n = 47)	13 (27.7)	10 (21.3)	3 (6.4)
Prevalence of extended-spectrum cephalosporin nonsusceptibility[a]			
Category (No. of isolates)	**Total nonsusceptible isolates (%)**	**ESC-I[d] (%)**	**ESC-R[e] (%)**
Hospital A (n = 247)	44 (17.8)	42 (17.0)	2 (0.8)
Hospital B (n = 29)	3 (10.3)	3 (10.3)	0 (0.0)
Hospital C (n = 100)	10 (10.0)	5 (5.0)	5 (5.0)
Hospital D (n = 47)	3 (6.4)	3 (6.4)	0 (0.0)

[a]*Confirmed by MIC test.*

[b]*PCN-I, penicillin intermediate (0.10 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[c]*PCN-R, penicillin high-level resistant (MIC ≥ 2.00 μg/ml).*

[d]*ESC-I, extended-spectrum cephalosporin intermediate (0.50 μg/ml ≤ MIC ≤ 1.00 μg/ml).*

[e]*ESC-R, extended-spectrum cephalosporin high-level resistant (MIC ≥ 2.00 μg/ml).*

[f]*Prevalence was higher in Hospital A than in Hospital C (χ^2 $P < 0.001$) or D (χ^2 $P = 0.001$).*

was 17.6%. The prevalence of ESC-N in urban counties decreased from 1998 (20.5, χ^2 $P = 0.04$). The prevalence of LEV-N in 2000, based on the MIC test result data, was 0.8%.

Rural Counties. Twenty-six laboratories from 22 rural counties in South Carolina responded to the survey. The prevalence of PCN-N in 2000 was 36.2%. The prevalence of PCN-N in rural counties increased from 1998 (29.9%, χ^2 $P = 0.04$). According to ESC MIC test results, the prevalence of ESC-N was 17.9% in 2000. The prevalence of ESC-N increased from 1998 (14.7%) to 2000, but it was not significant (χ^2 $P = 0.18$). The prevalence of LEV-N in 2000, as indicated by MIC results, was 0.8%.

Prevalence by Public Health District

South Carolina's 46 counties are divided into 13 public health districts. It was possible to calculate PCN-N (Fig. 1) and ESC-N (Fig. 2) prevalence data for 11 of the 13 districts. For health district PCN-N prevalence calculations, the sample size of isolates ranged between 17 and 562, and the median sample size of isolates was 106. For health district ESC-N prevalence calculations, the sample size of isolates ranged between 17 and 562, and the median sample size of isolates was 72. There were not enough data to calculate the prevalence of LEV-N by health district.

Discussion

This study indicates a high prevalence of PCN-N (38.4%), ESC-N (17.7%), and LEV-N (0.8%) among *S. pneumoniae* isolates in South Carolina in 2000. These results are similar to or higher than recent CDC pneumococcal surveillance system data. The CDC's Active Bacterial Core Surveillance, which includes eight states (California, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee), reported the following prevalences in 2000: PCN-N, 27.4%; cefotaxime nonsusceptibility, 17.8%; and LEV-N, 0.3%.[14]

The prevalence of PCN-N, ESC-N, and LEV-N does not appear to be geographically uniform in South Carolina. The prevalence of both PCN-N (range, 21.7–64.7%) and ESC-N (range, 8.5–30.6%) varied greatly among health districts. Each health district has a population of 200,000 or more. The geographic variation in the prevalence of PCN-N and ESC-N found in this study emphasizes the importance of community-based surveillance of pneumococcal susceptibility to antibiotics. We suggest a population-based approach because the

data show that the prevalence of DRSP can vary by district and even by hospitals within the same county (Table 4). These findings have been reported in other studies, which also recommend a population-based approach to antibiotic resistance surveillance.[15]

Because penicillin susceptibility cannot be assumed, all pneumococcal isolates associated with disease should be screened routinely for penicillin susceptibility by disk diffusion using a 1-μg oxacillin disk, which is highly sensitive for PCN-N. This study indicated that only 42.6% of responding clinical microbiology laboratories in South Carolina screen pneumococcal isolates with an oxacillin disk for penicillin nonsusceptibility. However, a majority of laboratories in South Carolina perform an MIC test only, instead of an oxacillin disk screening test followed by an MIC test.

Screening cannot reliably quantify the degree of PCN-N. Therefore, pneumococcal isolates with oxacillin zone sizes $\leq$19 mm should be tested by an MIC test method for PCN-N. This study indicated that 54.1% of clinical microbiology laboratories responding to the survey perform an MIC test on pneumococcal isolates to verify PCN-N. All probable DRSP isolates should also be tested by an MIC method for ESC-N and LEV-N.

Limitations

The survey design had two limitations. The first limitation is reporting bias. The survey results, including the MIC test results, were self-reported by the individual clinical microbiology laboratory. Screening test utilization and MIC testing methodologies varied by laboratory. In addition, the experience of personnel conducting these tests varied by laboratories. This project did not collect and test isolates to validate reported results. Second, we assumed the prevalence in a clinical laboratory's catchment population could serve as an accurate estimate of the prevalence of the public health district in which the laboratory is located.

Conclusions

The laboratory survey is a relatively low-cost method of estimating the prevalence of DRSP in South Carolina. It may serve as a model for other states where clinical laboratories routinely perform drug-susceptibility testing, but available resources to collect and test isolates centrally are limited. The prevalence estimates provided are sufficient to guide health care providers in selecting appropriate empiric therapy for suspected pneumococcal infections. Due to the high rates of resistance, South Carolina health care providers should consider the possibility of PCN-N, ESC-N, and LEV-N when treating suspected *S. pneumoniae* infections.[12]

Screening pneumococcal isolates for drug-resistance should be routine in clinical microbiology laboratories. The NCCLS recommends appropriate methods for susceptibility testing of pneumococcal isolates. For clinically important strains of *S. pneumoniae*, the NCCLS recommends routine screening of penicillin by the oxacillin disk diffusion method (Kirby-Bauer) for isolates from nonsterile sites (eg, nasopharyngeal, middle ear). Isolates from CSF or blood should go directly to the MIC method. Testing of penicillin, cefotaxime or ceftriaxone, meropenem, and vancomycin should be reported routinely for CSF isolates of *S. pneumoniae*. Penicillin, cefotaxime, ceftriaxone, and meropenem should be tested by a reliable MIC method. Vancomycin may be tested using MIC or disk method.

Present intervention strategies have yet to identify how much of a reduction is necessary in antimicrobial usage to reverse the increase in antibiotic resistance, or whether a reduction in pneumococcal resistance is achievable. However, prevalence data permit improved prescribing representing the patient's best interest, with judicious use of antibiotics favorably impacting morbidity and resistance. A number of prevention strategies should be promoted to decrease infections with DRSP in South Carolina, including adherence to the Advisory Committee for Immunization Practices recommendations regarding use of the 23-valent pneumococcal polysaccharide vaccine for persons 2 years of age or older with increased risk for pneumococcal disease[16]; use of Prevnar, the 7-valent pneumococcal conjugate vaccine, among children less than 2 years of age; and continuation of the statewide Careful Antibiotic Use Program.

References

1. Centers for Disease Control and Prevention. Defining the public health impact of drug-resistant *Streptococcus pneumoniae:* Report of a working group. *MMWR Recomm Rep* 1996;45(RR-1 Suppl):1–20.
2. Centers for Disease Control and Prevention. Assessment of national reporting of drug-resistant *Streptococcus pneumoniae*–United States, 1995–1996. *MMWR Morb Mortal Wkly Rep* 1996;45:947–949.
3. Macias EA, Mason EO Jr, Ocera HY, et al. Comparison of E test with standard broth microdilution for determining antibiotic susceptibilities of penicillin-resistant strains of *Streptococcus pneumoniae*. *J Clin Microbiol* 1994;32:430–432.
4. Spika JS, Facklam RR, Plikaytis BD, et al. Antimicrobial resistance of *Streptococcus pneumoniae* in the United States, 1979-1987: The Pneumococcal Surveillance Working Group. *J Infect Dis* 1991;163:1273–1278.
5. Nuorti JP, Butler JC, Crutcher JM, et al. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. *N Engl J Med* 1998;338:1861–1868.
6. Block SL, Harrison CJ, Hedrick JA, et al. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: Risk factors, susceptibility patterns and antimicrobial management. *Pediatr Infect Dis J* 1995;14:751–759.
7. Centers for Disease Control and Prevention. Prevalence of penicillin-resistant *Streptococcus pneumoniae:* Connecticut, 1992–1993. *MMWR Morb Mortal Wkly Rep* 1994;43:216–217, 223.
8. McGowan JE Jr, Metchock BG. Penicillin-resistant pneumococci: An emerging threat to successful therapy. *J Hosp Infect* 1995;30(Suppl):472–482.
9. Poole MD. Otitis media complications and treatment failures: Implications of pneumococcal resistance. *Pediatr Infect Dis J* 1995;14(4 Suppl):S23–S26.

10. Duchin JS, Breiman RF, Diamond A, et al. High prevalence of multidrug-resistant *Streptococcus pneumoniae* among children in a rural Kentucky community. *Pediatr Infect Dis J* 1995;14:745–750.

11. Breiman RF, Butler JC, Tenover FC, et al. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831–1835.

12. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: Management and surveillance in an era of pneumococcal resistance—a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J* 1999;18:1–9.

13. Office of Research and Statistics, South Carolina State Budget and Control Board. *1996 Statistical Abstract*. Columbia, Office of Research and Statistics, South Carolina State Budget and Control Board, 1996.

14. Centers for Disease Control and Prevention. *Active Bacterial Core Surveillance (ABCs) Report: Emerging Infections Program Network*—Streptococcus pneumoniae, *2000*. Atlanta, GA, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/dbmd/abcs/survreports/spneu00.pdf. Accessed July 2, 2003.

15. Quale J, Landman D, Ravishankar J, et al. *Streptococcus pneumoniae,* Brooklyn, New York: Fluoroquinolone resistance at our doorstep. *Emerg Infect Dis* 2002;8:594–597.

16. Heffernan R, Henning K, Labowitz A, et al. Laboratory survey of drug-resistant *Streptococcus pneumoniae* in New York City, 1993–1995. *Emerg Infect Dis* 1998;4:113–116.

Lord, help me to realize
That one warm embrace
Or one loving touch of the hand
May be able to release more healing
Than a bucketful of pills and medicine.

—Mark Link